Remarks

Claims 1-16 are pending.

Rejection Under 35 U.S.C. §103 - Claims 1-12

On page 4 of the December 27, 2006 Office Action, the Examiner rejected claims 1-12 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Youdim (WO 95/11016) in view of Kaal et al. (Journal of Neurochemistry, 2000, 74(3) pp. 1158-1165). Specifically, the Examiner alleged that Youdim et al. teach Applicant's active agent, R(+)-N-propargyl-1-aminoindan (Rasagiline) useful for the treatment of a neurodegenerative disease. The Examiner further alleged that Youdim et al. teach the therapeutically effective amount of Rasagiline to be 0.1 mg to about 100 mg, which is encompassed by the applicants amounts set forth in claims 4 and 12. In addition, the Examiner alleged that Youdim et al. teach pharmaceutically acceptable salts of Rasagiline. The Examiner did, however, acknowledge that Youdim et al. do not teach the treatment of amyotrophic lateral sclerosis (ALS) further comprising 2-amino-6-trifluoromethoxy benzothiazole (Riluzole) and its amounts.

On page 4 of the December 27, 2007 Office Action, the Examiner alleged that Kaal et al. teach that ALS is a neurodegenerative disease characterized by selective motor neuron death and that Kaal et al. teach that Riluzole is a drug currently used for treatment of ALS. The Examiner alleged that it would have been obvious to one of ordinary skill in the art to employ Rasagiline for the treatment of ALS because Youdim et al. teach that Rasagiline is useful for the treatment of a neurodegenerative disease and because Kaal et al. teach that ALS is a neurodegenerative disease. The Examiner alleged that one would have been motivated to employ Rasagiline for the treatment of ALS

in order to achieve an expected benefit or well-known efficacy in treating a neurodegenerative disease which includes ALS as taught by Kaal et al. The Examiner alleged that there is a reasonable expectation of successfully treating ALS by employment of Rasagiline because Rasagiline is effective for the treatment of neurodegenerative diseases which includes ALS as taught by Kaal et al.

On page 5 of the December 27, 2007 Office Action, the Examiner alleged that it would have been obvious to one of skill in the art to combine riluzole in its therapeutic amounts with rasagiline for the treatment of ALS because each of the active agent, particularly riluzole is a drug currently used for the treatment of neurodegenerative diseases such as ALS, and because Rasagiline is useful for treating neurodegenerative diseases which also includes ALS. It is the Examiner's opinion that one would have been motivated to combine riluzole and Rasagiline in a single formulation for the treatment of ALS in order to achieve an expected additive effect of treating neurodegenerative diseases including ALS.

Applicants Response:

In response, Applicants submit that the use of rasagiline (claims 1-4) for the treatment of ALS is neither taught nor suggested by the prior art, nor does the prior art provide any expectation that rasagiline would treat ALS.

Furthermore, Applicants submit that the use of rasagiline and riluzole together (claims 5-12) for the treatment of ALS is neither taught nor suggested by the prior art, nor does the prior art provide any expectation that the use of rasagiline and riluzole together would treat ALS.

Introduction

Applicants claim a method of using rasagiline to treat ALS, and a method of using rasagiline with riluzole to treat ALS. Thus, in the former method, Applicants seek to patent a new use for rasagiline, and in the latter method Applicants seek to patent combination therapy involving rasagiline and riluzole. The new use and the combination therapy are both unobvious in view of the prior art, each for reasons as discussed below.

M.P.E.P. 2112.02 states that, "the discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using." *Loctite Corp.* v. *Ultraseal Ltd.*, 781 F.2d 861, 875, 228 USPQ 90, 99 (Fed. Cir. 1985) determined that "Even if a composition is old, a process using a known composition in a new and unobvious way may be patentable." Combination therapy is also patentable if the combination is unobvious.

In order to establish a *prima facie* case of obviousness, it must be shown through explicit analysis that the claimed invention is no more than the "predictable use" of the prior art. *KSR v. Teleflex*, 550 U.S. _____ (2007). Applicants respectfully submit that the effects of rasagiline on ALS, and of the combination treatment on ALS, could not be predicted from the prior art.

I) One of skill in the art would not reasonably expect to be able to successfully treat ALS with Rasagiline

Prior to Applicants' invention, rasagiline had been neither taught nor suggested as a treatment for ALS. Certainly, nothing in the prior art provided any expectation that rasagiline would be an effective treatment for ALS, the effects of rasagiline on

ALS could not be predicted from the prior art.

First, contrary to the Examiner's position it is unclear whether ALS is a neurodegenerative disease; Youdim et al. do not include ALS in their list of neurodegenerative diseases. Moreover, Williams (BMJ, "Defining Neurodegenerative Diseases", 2002, 324: 1465-1466) describes that "neurodegeneration is a major element and is often the cause of the disability in many diseases not usually classified as degenerative - for example, multiple sclerosis, epilepsy, some inborn errors of metabolism, schizophrenia, and even tumors. Conversely, inflammatory processes are activated and vascular compromise occurs in some degenerative diseases. A Napoleonic view could encompass most brain diseases under the rubric of neurodegenerative, but this would lack focus. Few health authorities run services for neurodegenerative disease as a whole because they can cut across several subspecialties."

Second, it is unreasonable to expect a Parkinson's disease treatment to also successfully treat ALS. On the contrary, there is evidence in the prior art that ALS cannot be treated by a common Parkinson's disease treatment. Amantadine (Symmetrel) is used in combination with L-dopa to treat Parkinson's disease, however amantadine was found ineffective in ALS (Munsat, T.L. (1981) "Amantadine and guanidine are ineffective in ALS" Neurology 31:1054, copy submitted with accompanying Information Disclosure Statement).

Therefore, it is unreasonable and improper for the December 27, 2006 Office action to assert that one of skill in the art would have "expected benefit or well-known efficacy in treating" ALS with rasagiline. There is no evidence in the December 27, 2006 Office Action to support such a statement; in fact there is

evidence to the contrary. Thus, based on evidence with another Parkinson's disease treatment amantadine(Symmetrel), rasagiline would not be expected to effectively treat ALS.

Finally, the failed attempt to treat ALS with amantadine (Symmetrel) would instill one of skill in the art with the expectation that Parkinson's disease treatments are ineffective to treat ALS. Thus, the failed attempt with amantadine (Symmetrel) is a clear teaching away from Applicants' claimed invention. It is well settled that "when the prior art teaches away" from the claimed invention, the claimed invention is not obvious. See, e.g. *KSR v. Teleflex*, 550 U.S. _____ (2007), citing *U.S. v. Adams*, 383 U.S. 39, 40 (1966).

In conclusion, only a small number of pharmaceutical treatments are available to slow the progression of ALS, and until the disclosure of this invention, none were also known effective treatments for Parkinson's disease. Thus, there is nothing in the prior art to suggest that Parkinson's and ALS could be treated by rasagiline. Accordingly, the rejection under 35 U.S.C. §103 is improper and should be withdrawn.

II) The Combination of Rasagiline and Riluzole for the Treatment of ALS also Would not Have Reasonably Been Expected to be Successful by One of Skill in the Art Based on the Prior Art.

In addition to the uncertainties discussed above, one of skill in the art would recognize that combining rasagiline with riluzole would add yet another layer of uncertainty.

Applicants direct the Examiner to page 4, line 22 through page 5, line 27 of the subject specification for a discussion of the uncertainties individuals of skill in the art, i.e. the U.S. Food

and Drug Administration, recognized with combination therapy. Essentially, one of skill in the art would find the interactions between two drugs when administered together to treat a disease to be wholly unpredictable. Specifically:

> The *in vivo* interactions between two drugs, such as those of the subject invention, are complex. The effects of a drug are related to its absorption, distribution, and elimination. When two drugs are introduced into the body, each drug can affect the absorption, distribution, and elimination of the other and hence, alter the effects of the other. For instance, one drug may inhibit, activate or induce the production of enzymes involved in a metabolic route of elimination of the other drug ("Guidance for Industry"). Thus, when two drugs are administered to treat the same disease, it is unclear whether each will complement the therapeutic activity of the other, have no effect, or interfere with the therapeutic activity of the other.
>
> Not only may the interaction between two drugs affect the intended therapeutic activity of each drug, but the interaction may increase the levels of toxic metabolites ("Guidance for Industry"). The interaction may also heighten or lessen the side effects of each drug.
>
> Additionally, it is difficult to predict when the effects of the interaction between the two drugs will become manifest. For example, metabolic interactions between drugs may become apparent upon the initial administration of the second drug, after the two have

> reached a steady-state of concentration or even upon discontinuation of one of the drugs ("Guidance for Industry").
>
> Thus, the success of one drug or each drug separately in an *in vitro* model, an animal model or even in humans may not translate into success of the administration of both drugs in humans.

Therefore, the prior art would not have motivated one of skill in the art to combine riluzole with rasagiline to treat ALS. Moreover, one of skill in the art would have readily understood the uncertainties associated with combination therapy. Accordingly it is improper to reject applicants' pending claims under 35 U.S.C. §103 and such rejection should be withdrawn.

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following documents which are listed on Form PTO-1449 **(Exhibit A)** and are also listed below.

This Supplemental Information Disclosure Statement is being submitted after the mailing of the first Office Action but before the mailing date of a final Office Action. Under C.F.R. §1.97(c) and §1.17(p), the fee for filing an Information Disclosure Statement after the mailing of the first Office Action on the merits but prior to the mailing of a final Office Action is ONE HUNDRED EIGHTY DOLLARS and a check including this amount is enclosed. Accordingly, applicants request that this Information Disclosure Statement be considered.

Reference items 1-12 are either U.S. Patents or U.S. Patent Application Publications. Pursuant to 37 C.F.R. §1.98(a)(2), copies of references 1-12 are not being submitted.

Reference items 13 and 14 are unpublished U.S. patent applications. Pursuant to 37 C.F.R §1.98(a)(2)(iii), copies of the application specification including the claims corresponding to references 13 and 14, are attached hereto as **Exhibits 1** and **2**, respectively.

A copy of the documents listed herein as items 15-28 are attached hereto as **Exhibits 3-16**.

1. U.S. Patent No. 3,513,249, issued May 19, 1970 to Gittos et al.;

2. U.S. Patent No. 5,486,541, issued January 23, 1996 to Sterling et al.;

3. U.S. Patent No. 6,126,968, issued October 3, 2000 to Peskin et al.;

4. U.S. Patent No. 6,277,886, issued August 21, 2001 to Levy et al.;

5. U.S. Patent No. 6,630,514, issued October 7, 2003 to Youdim et al.;

6. U.S. Patent No. 6,635,667, issued October 21, 2003 to Thomas;

7. U.S. Patent No. 6,956,060, issued October 18, 2003 to Youdim et al.;

8. U.S. Published Application No. US 2004/0052843, published March 18, 2004 to Lerner et al.;

9. U.S. Published Application No. US 2005/0093830 A1, published May 5, 2005 to Youdim et al.;

10. U.S. Published Application No. 2006/0018957, published January 26, 2006 to Lerner et al.;

11. U.S. Published Application No. 2006/0094783 A1, published May 4, 2006 to Youdim et al.;

12. U.S. Published Application No. 2006/0188581 A1, published August 24, 2006 to Peskin;

13. U.S. Application No. 11/595,726, filed November 10, 2006 (Youdim et al.) **(Exhibit 1, specification and pending claim set is attached)**;

14. U.S. Serial No. 11/600,561, filed November 15, 2006 (Frenkel et al.) **(Exhibit 2, specification and pending claim set is attached)**;

15. PCT International Application No. WO 95/18617, published July 13, 1995 **(Exhibit 3)**;

16. PCT International Application No. WO 96/37199, published November 28, 1996 **(Exhibit 4)**;

17. PCT International Application No. WO 97/12583, published April 10, 1997 **(Exhibit 5)**;

18. PCT International Application No. WO 98/02152, published January 22, 1998 **(Exhibit 6)**;

19. PCT International Application No. WO/2006/057912, published June 1, 2006 **(Exhibit 7)**;

20. European Patent No. 0 436 492 A2, published June 8, 1994 **(Exhibit 8)**;

21. European Patent No. 0 538 134, published April 21, 1993 **(Exhibit 9)**;

22. Finberg et al., (1981) "Selective Irreversible Propargyl Derivative Inhibitors of Monoamine Oxidase (MAO) without the Cheese Effect" Chem. Abstracts 94:202499 **(Exhibit 10)**;

23. Finberg and Youdim, (1985) "Modification of Blood Pressure

and Nictitating Membrane Response to Sympathetic Amines by Selective Monoamine Oxidase Inhibitors" Brit. J. Pharmac. 541-546 **(Exhibit 11)**;

24. Finberg et al. (1985) "Modification of Blood Pressure and Nictitating Membrane Response to Sympathetic Amides by Selective Monoamide Oxidase Inhibitors, Types A and B, in the Cat" Chem. Abstracts 103:81618 **(Exhibit 12)**;

25. Mendleicz and M.B.H. Youdim (1987) Brit. J. Psychiat. 142:508-511 **(Exhibit 13)**;

26. Youdim et al.(1984) Progress in Medical Chemistry 21:138-167 **(Exhibit 14)**;

27. Youdim et al. (1988) Handbook of Experimental Pharmacology Vol. 90/I (1988) Chapter 3 Trendlenburg and Weiner, eds. **(Exhibit 15)**; and

28. Munsat, T.L. (1981) "Amantadine and guanidine are ineffective in ALS" Neurology 31:1054 **(Exhibit 16 - Abstract only)**.

Applicants request that the Examiner review the publications and make them of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorneys invite the Examiner to telephone at the number provided below.

No fee, other than $180.00 for filing an Information Disclosure Statement and $450.00 for a two-month extension of time, is deemed necessary in connection with the filing of this communication. However, if any other fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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Gary J. Gershik 5/27/07
John P. White Date

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EXHIBIT A
Applicants: Eran Blaugrund et al.
Serial No.: 10/712,958
Filed: November 13, 2003